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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/574,666	04/04/2006	Mannalal Ramgopal Bajaj	125139-00101	9001

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EXAMINER	
LEA, CHRISTOPHER RAYMOND	
ART UNIT	PAPER NUMBER
1613	
MAIL DATE	DELIVERY MODE
10/29/2010	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/574,666	BAJAJ ET AL.	
	Examiner	Art Unit	
	Christopher R. Lea	1613	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 August 2010*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,9,10,12 and 16-18* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,9,10,12 and 16-18* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

This application is a 371 (national stage application) of PCT/IN04/00342.

Receipt of Amendments/Remarks filed on August 23, 2010, is acknowledged. In response to non-final Office Action dated March 22, 2010, applicant amended claim 1, canceled claim 7, and added no new claims. Claims 1, 9, 10, 12, & 16-18 are pending. Claims 1, 9, 10, 12, & 16-18 are under examination.

Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. All new rejections applied have been necessitated by applicant's amendment to the claims. They constitute the complete set presently being applied to the instant application.

Claim Rejections - 35 USC § 112

1. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2. Claim 18 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. While the ratio of rabeprazole sodium to sodium hydroxide in the first column of the table can computed to be 1:0.359, such does not

reasonably convey to one of ordinary skill in the art that applicant was in possession of the invention of claim 18. The table provides the exact value, so the support for "about" 1:0.359 is not explicit; as such, the use of the term "about" constitutes new matter.

Claim Rejections - 35 USC § 103

3. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

4. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

5. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to

consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

6. Claims 1, 9, 10, 12, & 16-18 are rejected under 35 U.S.C. 103(a) as being unpatentable over Doen et al. (US PreGrant Publication 2003/0191157) in view of Nakanishi et al. (US Patent 5,589,491).

Applicant claims

Applicant claims a drug delivery system containing rabeprazole sodium, mannitol, an alkaline compound and water for injection. Applicant further teaches a method of making such a system.

Determination of the scope and content of the prior art (MPEP 2141.01)

Doen et al. teach, as a whole, an injectable composition containing a benzimidazole.

Claim 1: Doen et al. teach an injectable composition containing a benzimidazole compound and an alkaline compound in a molar ratio of about 1:1 (paragraph 35). Doen et al. teach rabeprazole sodium among the benzimidazole compounds suitable for use in the injectable composition (paragraph 76). Doen et al teach that sodium hydroxide is the preferred alkaline compound suitable for use in the injectable composition (paragraph 86). Doen et al. teach that a saccharide may be added to the composition as an excipient and that mannitol is the preferred excipient suitable for use in the injectable composition (paragraph 91). Doen et al. teach water for injection as a solvent for

dissolving (paragraph 99) or redissolving (paragraph 110) the composition. Doen et al. teach the pH of the composition as about 9 to 11 in physiological saline (paragraph 99).

Claims 9 & 16: Doen et al. teach a composition that contains ~29% benzimidazole compound (Example 3, Table 4, paragraph 132).

Claims 10 & 17: Doen et al. teach a composition that contains ~58% excipient (Example 3, Table 4, paragraph 132).

Claims 18 & 12: Doen et al. teach adding a benzimidazole compound and mannitol to a sodium hydroxide solution and adding water for injection (paragraph 128, changing the order of adding ingredients is *prima facie* obvious, MPEP § 2144.04.IV.C). Doen et al. teach rabeprazole sodium among the benzimidazole compounds suitable for use in the injectable composition (paragraph 76). Doen et al. teach sterile filtering the solution (through 0.22 micron filter) and placing it in vials (paragraphs 128-9). Though Doen et al. are silent as to the exact size of the vial and its sterility, they teach the vial size is under 20 mL (paragraph 106) and it would have been obvious to a skilled artisan to put a sterile filtered solution into a sterile vial and bunging the vial to maintain sterility. Doen et al. are silent as to the temperature at which the steps are carried out; however, the maintaining a constant temperature is within the purview of the skilled artisan. Doen et al. teach lyophilizing the solution to form a powder (paragraph 132). The resultant composition meets the limitations of claim 12.

Ascertainment of the difference between the prior art and the claims (MPEP 2141.02)

The difference between the teachings of Doen et al. and the instant claims is that Doen et al. do not exemplify an embodiment of the invention using rabeprazole sodium in the claimed molar ratio. This deficiency in Doen et al. is cured by the teachings of Nakanishi et al.

Nakanishi et al. teaches, as a whole, injectable formulations of benzimidazole compounds (abstract).

Nakanishi et al. teaches an injectable formulation containing water for injection, sodium hydroxide and omeprazole (a benzimidazole of the same family possessing similar proton pump inhibiting activity) with a pH of 11.5 where the ratio of benzimidazole active agent to alkaline agent is 1:0.0397 (example 1, table 4).

Finding of *prima facie* obviousness
Rationale and Motivation (MPEP 2142-2143)

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made to use rabeprazole sodium as the benzimidazole and adjust the molar ratio of alkaline to rabeprazole sodium and produce the instant invention. The skilled artisan would have been motivated to use rabeprazole sodium as the benzimidazole because Doen et al. teach that it is suitable for that use and it is within purview of the skilled artisan to select a known material based on its suitability for its intended use. Reading a list and selecting a known compound to meet known requirements is no more ingenious than selecting the last piece to put in the last opening in a jig-saw puzzle (see MPEP § 2144.07). The skilled artisan would have been motivated to adjust the ratio of rabeprazole sodium to alkaline compound because Doen

et al. although the preferred ratio is 1:1, generally, differences in concentration will not support the patentability of subject matter encompassed by the prior art unless there is evidence indicating such concentration is critical. It is not inventive to discover the optimum or workable ranges by routine experimentation when the prior art discloses the general conditions of a claim (See MPEP 2144.05 II). Further, the teachings of Nakanishi et al. clearly demonstrate that a ratio lower that 1:1 is not only feasible, but has a high expectation of success. Additionally, the combined teachings of Doen et al. and Nakanishi et al. disclose a range of the ratio of benzimidazole to sodium hydroxide of 1:1 to 1:0.0397 which encompasses (and renders obvious) the claimed ratio (See MPEP § 2144.05 I)

From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in using rabeprazole sodium as the benzimidazole and adjusting the molar ratio of alkaline to rabeprazole sodium and producing the claimed invention. Therefore, the invention as a whole would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

In light of the forgoing discussion, one of ordinary skill in the art would have concluded that the subject matter defined by the instant claims would have been obvious within the meaning of 35 USC 103(a).

Response to Arguments

7. Applicant's arguments filed August 23, 2010, have been fully considered but they are not persuasive.

The examiner has previously held that the declaration under 37 CFR 1.132 filed December 15, 2009, is insufficient to overcome the rejection of claims 1, 9, 10, 12, & 16-18 based upon Doen et al. in view of Nakanishi et al. applied under 35 U.S.C. 103 as set forth in the last Office action for a number of deficiencies. Applicants have attempted to supplement the December declaration with an additional declaration (the August declaration). This August declaration cures some of the deficiencies of the December declaration; however, it still fails to establish "that the differences in results are in fact unexpected and unobvious and of both *statistical and practical* significance."(emphasis added, See MPEP 714.02(b) I). The declaration shows that the rabeprazole in the A sample goes from 100.9% to 98.6% (2.3% decrease) and in the B sample goes from 97.6% to 91% (6.6% decrease) after 1 hour following reconstitution. No description of the method for the determination of these percentages is described, so it is unclear whether the differences are within the limits of detection and quantification for the assay (i.e. its sensitivity) and without the standard deviation of the measurements it is impossible to determine if and to what level of confidence the results may be said to be actually different. Without such information one of ordinary skill in the art would not be able to determine if the differences shown are differences of degree or kind. Applicants argue (in both the remarks and the August declaration) that the protocol clearly specifies that the standard deviation is no more than 2%. The August declaration states

that the protocol is attached as Appendix A; however, the examiner cannot find said Appendix in the file wrapper and the EFS receipt does not show that it was submitted. Without this protocol, the examiner has no way of verifying that the protocol has the level of significance applicant argues. As such, the declaration is still unconvincing.

Further, the examiner questions whether the results applicant asserts as unexpected are really unexpected. Applicant argues that the claimed ratio of rabeprazole to sodium hydroxide provides unexpected stability. The underlying premise of this argument is that rabeprazole degrades in the presence of high alkaline conditions (such as 1:1 ratio of Doen et al.). The examiner, in his role as fact-finder, has found that this premise is flawed. Buchireddy et al. (Chromatographia 68(3-4): 275-280) teach that rabeprazole is not susceptible to degradation when subjected to alkaline hydrolysis with 0.5 M NaOH (p. 278, “Forced degradation” and p. 279, Table 2). Given that Buchireddy et al. establish as scientific fact that rabeprazole is not susceptible to alkaline hydrolysis, the claimed ratio of rabeprazole to sodium hydroxide cannot be responsible for the increased stability that applicant asserts is present.

The expected result remains the same; an injectable formulation of rabeprazole is made in the absence of evidence to the contrary. No unexpected results have been presented. Applicant's arguments are not persuasive; and the rejection under 35 U.S.C. §103(a) is maintained.

Conclusion

Claims 1, 9, 10, 12, & 16-18 are rejected. No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Christopher R. Lea whose telephone number is (571) 270-5870. The examiner can normally be reached on Mon-Fri 7:30-3:30 ET.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brian Kwon can be reached on (571)272-0581. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only.

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/Ernst V Arnold/
Primary Examiner, Art Unit 1613

/C. R. L./
Examiner, Art Unit 1613

crl